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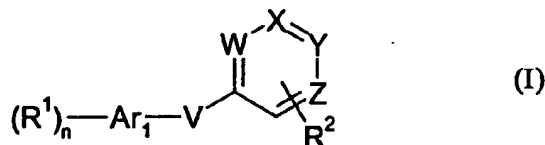
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[Continued on next page]

(54) Title: AMINO-HETEROCYCLES AS VR-1 ANTAGONISTS FOR TREATING PAIN



(57) Abstract: the present invention provides a compound of formula (I): wherein V represents NR<sup>5</sup>, O, S, SO or S(O)<sub>2</sub>; W and X each independently represent CH or N; Y represents N, CH or C-Ar<sub>2</sub>, with the proviso that at least one, but no more than two, of W, X and Y are N; Z represents CH or C-Ar<sub>2</sub>, with the proviso that when Y is N or CH then Z is C-Ar<sub>2</sub>, and with the further proviso that when Y is C-Ar<sub>2</sub> then Z is CH; Ar<sub>1</sub> represents a fused 9 or 10 membered heterobicyclic ring system containing one, two, three or four heteroatoms selected from nitrogen, oxygen and sulfur, wherein at least one of the rings in said ring system is aromatic; Ar<sub>2</sub> represents an aromatic ring selected from phenyl, pyridyl, pyrimidinyl and pyridazinyl which is optionally fused and substituted; R<sup>1</sup> represents halogen, hydroxy, oxo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, haloC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, hydroxyC<sub>1-6</sub>alkoxy, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkoxy, C<sub>3-5</sub>cycloalkylC<sub>1-4</sub>alkyl, cyano, nitro, SR<sup>6</sup>, SOR<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, COR<sup>6</sup>, NR<sup>3</sup>COR<sup>6</sup>, CONR<sup>3</sup>R<sup>4</sup>, NR<sup>3</sup>SO<sub>2</sub>R<sup>6</sup>, SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -(CH<sub>2</sub>)<sub>m</sub>carboxy, esterified -(CH<sub>2</sub>)<sub>m</sub>carboxy or -(CH<sub>2</sub>)<sub>m</sub>NR<sup>3</sup>R<sup>4</sup>; R<sup>2</sup> represents hydrogen, halogen, hydroxy, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, unsubstituted phenyl or phenyl substituted with one or two groups selected from halogen, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkoxy or haloC<sub>1-6</sub>alkoxy; R<sup>3</sup> and R<sup>4</sup> are each independently hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-7</sub>cycloalkyl or fluoroC<sub>1-6</sub>alkyl; or R<sup>3</sup> and R<sup>4</sup> and the nitrogen atom to which they are attached together form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C<sub>1-6</sub>alkoxy, which ring may optionally contain as one of the said ring atoms an oxygen or a sulfur atom, S(O), S(O)<sub>2</sub>, or NR<sup>5</sup>; R<sup>5</sup> represents hydrogen, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl; R<sup>6</sup> represents hydrogen, C<sub>1-6</sub>alkyl, fluoroC<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, unsubstituted phenyl, or phenyl substituted with one or two groups selected from halogen, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkoxy or haloC<sub>1-6</sub>alkoxy; m is either zero or an integer from 1 to 4; n is either zero or an integer from 1 to 3; or a pharmaceutically acceptable salt, N-oxide or a prodrug thereof; a pharmaceutical composition comprising it; its use

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KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB 03/04969

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 - C07D403/12 C07D401/14 C07D405/14 C07D471/04  
A61K31/4709 A61K31/4725 A61P29/00 //(C07D471/04, 235:00,  
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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 41508 A (EDWARDS PETER DAVID ;WARD ROBERT WILLIAM (GB); THOMPSON MERVYN (GB) 24 September 1998 (1998-09-24) claims	1-11
A	WO 02 08221 A (BAKTHAVATCHALAM RAJAGOPAL ;DESIMONE ROBERT W (US); NEUROGEN CORP ( ) 31 January 2002 (2002-01-31) cited in the application claims	1-11
P, A	WO 03 068749 A (MITCHELL DARREN JASON ;RAMI HARSHAD KANTILAL (GB); GLAXO GROUP LTD) 21 August 2003 (2003-08-21) claims	1-11
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*S\* document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 03/04969

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 03 080578 A (BROWN REBECCA ELIZABETH ;HOLLINGWORTH GREGORY JOHN (GB); LINDON MA) 2 October 2003 (2003-10-02) claims	1-11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 03/04969

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No  
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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9841508	A	24-09-1998	AU 737955 B2	06-09-2001
			AU 6412898 A	12-10-1998
			BR 9809047 A	01-08-2000
			CN 1255124 T	31-05-2000
			EP 0968190 A1	05-01-2000
			WO 9841508 A1	24-09-1998
			JP 2001515504 T	18-09-2001
			NO 994510 A	17-09-1999
			NZ 337424 A	31-08-2001
			PL 335676 A1	08-05-2000
			TR 9902283 T2	21-12-1999
			US 2003144320 A1	31-07-2003
			US 2001016657 A1	23-08-2001
			ZA 9802185 A	16-09-1999
			AU 744451 B2	21-02-2002
			AU 1572499 A	05-07-1999
			BG 104607 A	28-02-2001
			BR 9813642 A	17-10-2000
			CA 2315079 A1	24-06-1999
			CN 1125052 B	22-10-2003
			EP 1042296 A1	11-10-2000
			WO 9931068 A1	24-06-1999
			HU 0000987 A2	28-09-2000
			HU 0004663 A2	28-05-2001
			ID 24810 A	24-08-2000
			JP 2002508360 T	19-03-2002
			NO 20003142 A	16-06-2000
			NZ 504706 A	26-11-2002
			PL 341222 A1	26-03-2001
			SK 9142000 A3	07-11-2000
			TR 200001791 T2	21-12-2000
			US 6248754 B1	19-06-2001
			ZA 9811503 A	15-06-2000
WO 0208221	A	31-01-2002	AU 8066701 A	05-02-2002
			BR 0112631 A	23-09-2003
			CA 2415606 A1	31-01-2002
			CN 1443170 T	17-09-2003
			EP 1301484 A2	16-04-2003
			WO 0208221 A2	31-01-2002
			US 2002132853 A1	19-09-2002
WO 03068749	A	21-08-2003	WO 03068749 A1	21-08-2003
WO 03080578	A	02-10-2003	WO 03080578 A1	02-10-2003